The Ethics of Research Involving Human Subjects

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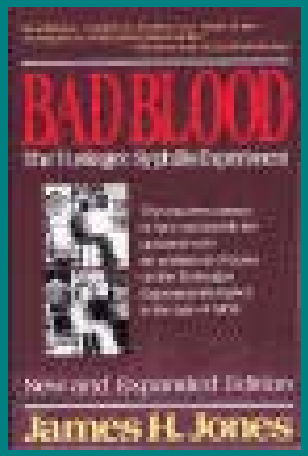
Ethical Standards for Research

- Background: Nazi experiments & the Nuremberg Code
- Standards in US were sharpened in the context of our own ethical scandals such as the Tuskegee syphilis study



The Belmont Principles

- *Beneficence*
- *Respect for Persons*
- *Justice*

Formulated by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Federal Register, 1979)

Respect for Persons

- Respect autonomous agents
- Protect persons with diminished autonomy
- Application: informed consent (information, comprehension, & voluntariness)

Beneficence

- Do not harm
- Maximize possible benefits and minimize possible harms
- Application: conduct analysis to determine that probable benefits outweigh risks

Justice

- Fair distribution of the benefits and burdens of research
- Application: fair selection of research subjects

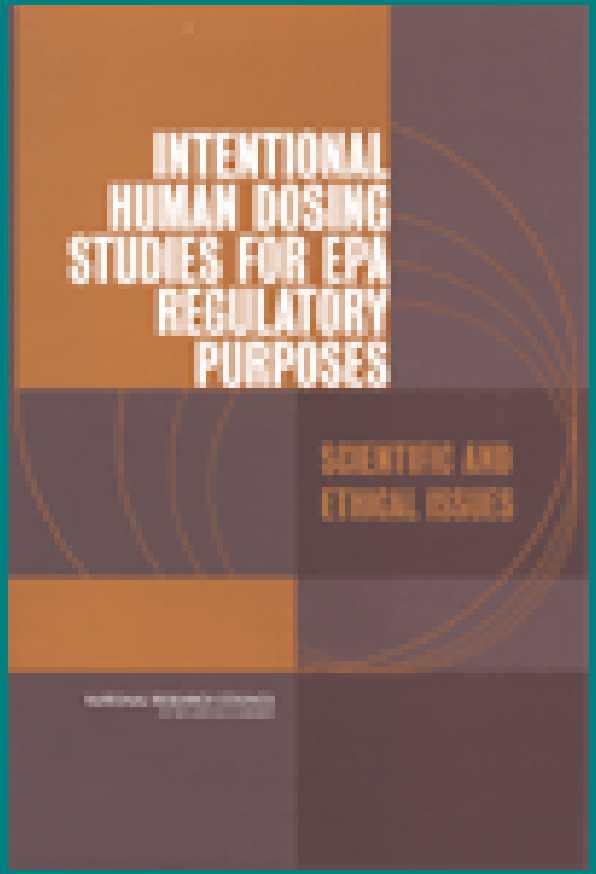
Implications for Third-Party Dosing Studies for EPA

- Widespread negative visceral reactions to intentional dosing studies for EPA regulatory purposes
- Yet some analogies between such studies and Phase I drug testing

National Research Council (NRC) Report (2004)

- Interdisciplinary committee, co-chaired by James Childress & Michael Taylor
- Report stresses an integrated review of science & ethics

http://books.nap.edu



NRC/NAS Committee

- Did not try to create ethical standards but instead applied existing standards
- In the *Federal Policy for the Protection of Human Subjects* (the "Common Rule") accepted by EPA & many other federal agencies
- In the *Belmont Report*, etc.

Two Pillars of Subject Protection

- Review by Institutional Review Board (IRB)
- Informed Consent

Common Rule: Criteria for IRB Approval of Research

- Minimization of risks to subjects
- Determination that risks are reasonable in relation to anticipated benefits
- Equitable selection of subjects
- Informed consent & its documentation
- Appropriate monitoring to ensure safety
- Protection of privacy and confidentiality

NRC: Criteria for Scientific & Ethical Acceptability (1)

a. Prior research: animal studies &, if available, human observational studies;
b. Need for the knowledge: demonstration of need for knowledge to be obtained;
c. Research design and statistical analysis: adequacy to address an important scientific or policy question;

NRC: Criteria for Scientific & Ethical Acceptability (2)

d. Acceptable balance of risks and benefits & minimization of risks to participants;
e. Equitable selection of participants
f. Free and informed consent by participants
g. IRB review (or foreign equivalent)

Elaboration of RBA (1)

- Possible societal benefits range from (A) improving accuracy of RfD to (B) providing public health or environmental benefits
- Research to improve scientific accuracy "can be justified only when there is reasonable certainty that participants will experience no adverse effects."

Elaboration of RBA (2)

- Research that will probably produce public health or environmental benefit can justify greater risks for participants
- But, even then, only if several other ethical conditions are also met

Participant Selection Criteria (1)

a. Equitable (fair, just) selection
b. Enrollment of persons from vulnerable populations
   -- must be convincingly justified
   -- and must be accompanied by protective measures

Selection Criteria (2)

c. Enrollment of individuals at increased risk for adverse effects

-- must be convincingly justified in the protocol

-- and must be accompanied by protective measures

Selection Criteria (3)

For children (vulnerable in both senses)

- EPA should adopt Subpart D of Regulations for the Protection of Human Research Subjects, or, at least, adhere to Subpart D
- The NRC committee views Subpart D's standards as quite stringent

Payment for Participation

- Should not be
  - So high as to be undue inducement
  - So low as to be attractive only to socio-economically disadvantaged persons
- Further federal agency consideration whether to pay for level of risk as well as time and inconvenience

Compensation for Research-related Injuries

- Participants should receive needed medical care for research-related injuries, without cost to them.
- In addition, EPA should study whether broader compensation for research-related injuries should be required.

Best Practices in Informed Consent

- EPA should develop and disseminate a list of best practices re IC
- EPA should encourage their adoption in third-party studies
- EPA should require their adoption in studies it sponsors or conducts

Review of Intentional Dosing Studies

- IRB review of all studies
- New Human Studies Review Board for integrated science-ethics review
  - Protocols in advance (voluntarily submitted)
  - Study results after completion

Data from Ethically Problematic Studies After New Standards

- Strong presumption against EPA consideration in regulatory decisions
- Exceptional case: where studies might "provide valid data to support a regulatory standard that would provide greater protection for public health"
- Evaluation by special, outside panel, with public members as well as experts

Studies Conducted Before New Standards (1)

- EPA should accept scientifically valid studies unless "clear and convincing evidence" that
  - Their conduct was fundamentally unethical (e.g., intention to inflict serious harm or failure to get informed consent) or
  - Their conduct was "deficient to then-prevailing ethical standards"

Studies Conducted Before New Standards (2)

- Exceptional case: where scientifically valid studies might "support a regulatory standard that would provide greater protection for public health"
- Procedure: Special, outside panel with public members as well as experts to evaluate the arguments for and against

Conclusion

- Ethical principles for research involving human subjects (participants) can justify intentional dosing studies if several conditions are met.
- These conditions should apply to both third-party studies and EPA-sponsored and conducted studies.